REMARKS

Claims 44 and 45 are now pending in the application. Claims 1-43 have been cancelled without prejudice. New claims 44 and 45 are now directed to the subject matter claimed in former claim 28 restricted however to specific oligonucleotides (SEQ ID NO: 22 and SEQ ID NO: 24) exemplified and supported. No new matter has been hereby introduced.

The Applicants respectfully submit that the claims now on file have been restricted to a method for the prophylaxis or treatment of specific viral infection comprising administering a formulation comprising SEQ ID NOs: 22 or 24. The viral infection encompassed by the new claims now on file are restricted to infection caused by virus families which the Applicants have data supporting the utility of the claimed subject matter. As disclosed in the present application in paragraph [0083] (page 20), the Applicants taught that the oligonucleotides disclosed in the present application, such as those recited in the sequence listing submitted January 19, 2005, have an antiviral activity against virus families claimed in new claims 44 and 45 submitted herewith.

More specifically, in regard to SEQ ID NO: 22 (REP 2031, C_{40} or polyC) data concerning its antiviral activity against viruses of the herpesviridae family were disclosed in paragraph [00302] (page 87) and figure 37a of the present application. *In vivo* data were presented in a previously submitted Declaration from Dr. Jean-Marc Juteau filed August 11, 2006. Furthermore, the Applicants previously presented *in vivo* data concerning the efficacy of SEQ ID NO: 22 to inhibit infection of viruses form the orthomyxoviridae family in the Declaration filed August 11, 2006. In addition, enclosed herewith is a further Declaration from Dr. Jean-Marc Juteau disclosing the *in vitro* and *in vivo* anti-viral activity of SEQ ID NO: 22 against viruses from the herpesviridae, hepadnaviridae, filoviridae, flaviridae, orthomyxoviridae, and paramyxoviridae family.

Concerning the efficacy of SEQ ID NO: 24 (REP 2055, AC_{20} or polyAC) to inhibit virus infections caused by viruses from the herpesviridae, hepadnaviridae and flaviridae family, the Applicants respectfully submits that data concerning its anti-viral activity against viruses of the herpesviridae family were disclosed in paragraph [00303] (page 88) and figure 37b of the present application. Enclosed herewith is a Declaration from Dr. Jean-Marc Juteau

disclosing the *in vitro* and *in vivo* anti-viral activity of SEQ ID NO: 24 against viruses from the herpesviridae and flaviridae family. Further, in the Declaration, *in vivo* data are also enclosed demonstrating the *in vivo* efficacy of SEQ ID NO: 24 to inhibit viral infection of viruses from the hepadnaviridae family.

Consequently, the Applicants clearly demonstrated a correlation of the anti-viral activity of SEQ ID NO: 22 and SEQ ID NO: 24 as now claimed, against viruses of specific families, *in vitro* and their efficacy *in vivo*, and thus a person skilled in the art is able to fully predict possible results of the clinical benefit of the claimed method only based on these results.

The Applicants wish to also submit that by the nature of the sequence of SEQ ID NOs: 22 and 24, these sequences are not complementary to the nucleic acid sequence of a gene of any virus, and thus the anti-viral activity of these oligonucleotides is occurring by a sequence independent mode of action. Contrary to the subject matter claimed in the present application and as acknowledged by the Examiner, Andreola *et al.* **only teach** a specific sequence having high affinity to RNAse H domain of HIV-1 RT. Nowhere is it taught or even suggested in Andreola *et al.* that oligonucleotides, specifically SEQ ID NO: 22 or SEQ ID NO: 24, may have an anti-viral activity against other viruses.

In addition, the Applicants wish to point out that the claims now on file are not anticipated or obvious in view of the teaching found in Andreola *et al.* and Peyman *et al.* In this regard, the Applicants submit that the Examiner, in her own arguments presented in the Final Office Action dated December 15, 2006, suggested that Andreola *et al.* not only teaches that "*oligonucleotides have antiviral activity due to the sequence*", but also discloses that sequences that fold "*into a pseudoknot motif were found to bind HIV-1 RT with high affinity*". On page 1, second column, lines 7 and 8, it is clearly stated in Andreola *et al.* that *"sequences folding into the pseudoknot motif were found to bind HIV-1 RT with high affinity."* In the same paragraph in Andreola *et al.*, it is disclosed that the SELEX technique was used to isolate an RNA with a pseudoknot structure known as the "Tuerk-type pseudoknot". By definition, and as recognized by a person skilled in the art, a "pseudoknot motif" is an RNA secondary structure containing two stem-loop structures in which the first stem's loop forms part of the second stem. A classical pseudoknot is formed through a base pairing interaction

between nucleotides in the loop of a stem loop and an adjacent single-stranded region. Consequently, in order to fold into a "pseudoknot", there is a need for specific nucleotides to be present in a stem loop and in an adjacent single-stranded region in order to allow pairing between the loop and the single-stranded region.

In regards to the "Tuerk-type pseudoknot", Andreola refers to the document of Tuerk *et al.* (1992; PNAS, 89: 6988-6992). A person skilled in the art, after analyzing the consensus pseudoknot motif known as the "Tuerk-type pseudoknot", would acknowledge that it is clearly a motif which is sequence dependent in order to fold properly and to bind HIV-1 RT. To the contrary, the Applicants respectfully point out that the anti-viral activity of SEQ ID NO: 22 and of SEQ ID NO: 24 is sequence independent.

The Applicants also add that the SELEX method is a protocol that involves the selection from random pools of RNA and DNA molecules of oligonucleotides able to strongly bind to protein as ligands (see Andreola *et al.*, page 5032, first column, second paragraph). These methods involves cycles of affinity selection by a protein from a heterogeneous population of DNA molecules, replication of bound species, *in vitro* transcription and reverse transcription to generate an enriched pool of bound DNA (Andreola *et al.*, page 5032, first and second column). In this regard, the Examiner specifically mentioned in the Final Office Action that "*the SELEX approach was also used to identify high affinity DNA ligands against HIV-1 RT... Although they showed little structural similarity to the RNA aptamers, they were able to bind the RT... and inhibited specifically the DNA polymerase activity...*". This quote was taken from Andreola *et al.*, page 5032, right column, second paragraph, who references Schneider *et al.* (1995, Biochemistry, 34: 9599-9610). If one analyses the document of Schneider *et al.*, clearly the SELEX method allowed isolating specific sequences of DNA (30 in total) that bind the HIV-1 RT. For example, it is clearly demonstrated that the 30 specific molecules, which had a unique sequence, could be classified into families according to common primary sequence elements (see Figure 2), and, for each family, a potential common secondary structure was generated (see Figure 3 in Schneider *et al.*). On the contrary, a person skilled in the art would acknowledge that the anti-viral activity of SEQ ID NO: 22 and SEQ ID NO: 24 is not due to an antisense mechanism or due to the complementarity of the sequence of these specific oligonucleotides to a viral

sequence. Consequently, the antiviral activity of SEQ ID NO: 22 and of SEQ ID NO: 24, as claimed in claims 44 and 45, is independent on the nature of the sequence, and thus not anticipated or obvious in view of the teaching found in Andreola *et al.*

The Applicants wish to also resubmit at this point that nowhere is it taught or even suggested in Peyman *et al.* that oligonucleotides have antiviral activity against multiple viruses acting by a sequence independent mode of action. Moreover, Peyman *et al.* only enabled four antisense oligonucleotides against HSV-1 in cell culture (as disclosed in column 14, lines 14-19 in Peyman). Peyman *et al.* only teaches how to stabilize and improve cell penetration by capping antisense oligonucleotides (with the addition of a cap of guanine at their extremities). Peyman *et al.* teaches in column 6, lines 8-9, that the effective oligonucleotides are understood to mean antisense oligonucleotides. By definition, an "antisense" is a molecule that interacts with complementary strands of nucleic acids, modifying the expression of genes. Consequently, a person skilled in the art would recognize that an antisense RNA or single-stranded antisense DNA is a molecule which is complementary to the nucleic acid sequence of a gene of interest. Thus, the mechanism of action of an antisense is sequence dependent since it must be complementary to a strand of a nucleic acid in order to interact and modify the expression of the gene of interest. In addition, such person skilled in the art would conclude that SEQ ID NOs: 1-34 disclosed by Peyman *et al.* represent sequences that are complementary to known genes, and thus represent antisense oligonucleotides. The Applicants previously submitted a Table identifying the gene targeted by these antisenses (see last response filed February 9, 2007). In column 6, lines 30-31; column 8, lines 29-30; column 10, lines 35-36; column 11, lines 4-5; and column 14, lines 14-19 of Peyman *et al.*, it is clearly stated that the oligonucleotides represented by SEQ ID NOs: 35-105 are examples of novel antisense effective against specific targets. All sequences listed in this patent are complementary to target sequences.

Consequently, SEQ ID NOs: 1-105 all represent antisense oligonucleotides which are complementary to a portion of the nucleic acid sequence of a specific gene. Thus, by definition, an antisense will modify the expression of a gene by a sequence dependent mode of action. This is reflected in the claims of Peyman *et al.* where an oligonucleotide having a nucleotide sequence complementary to a target sequence flanked by a Cap of guanines is

claimed. On the contrary, the Applicants submit that the present application teaches oligonucleotides having a sequence independent mode of action, as submitted hereinabove.

In addition, Peyman *et al.* discloses (in columns 1 and 2, under the Summary section), oligonucleotides having antiviral activity because they are antisenses and which have a Cap of guanine(s) at its 5' and/or 3' extremity to stabilize and improve cell penetration. To the contrary, the oligonucleotides disclosed in the present invention do not require being antisenses, nor do they need to have a Cap of guanines in order to have antiviral activity. Once again, a person skilled in the art would recognize that Peyman *et al.* teach antisense oligonucleotides wherein stabilization depends on the presence of a Cap of guanines and the antiviral activity depends on the sequence of the antisense oligonucleotide. Thus, the stabilization of the antisenses disclosed in Peyman is dependent on the presence of a secondary structure since, as stated in Peyman *et al.* (see column 1, lines 55-57), oligonucleotides which contain short segments of G residues are able to form intramolecular structures called G-quartets. Thus, not only is the antiviral activity dependent on the sequence, but the stabilization of the antisenses disclosed in Peyman is sequence dependent (in order to form the G-quartet structure). In view of the arguments presented hereinabove, it is believed that nowhere is it taught or even suggested in Peyman that SEQ ID NO: 22 and SEQ ID NO: 24 have an anti-viral activity which is sequence independent, and thus claims 44 and 45 now on file are novel and inventive in view of the teaching of Peyman *et al.*

It is submitted, therefore, that new claims 44 and 45 are in condition for allowance. Reconsideration of the Examiner's rejections is respectfully requested. Allowance of claims 44 and 45 at an early date is solicited.

No additional fees are believed to be necessitated by this amendment. Should this be in error, authorization is hereby given to charge Deposit Account No. 19-5113 for any underpayment or to credit any overpayment.

Commissioner of Patents
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In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application can be expedited.

Respectfully,

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